DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1440 B

WARNING LETTER

Food and Drug Administration
Center for Biologics Evaluation and Resear
1401 Rockville Pike
Rockville MD 20852-1448

February 24, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Andreas Gardi, Ph.D., Responsible Head
ZLB Central Laboratory
Blood Transfusion Service, Swiss Red Cross
Wankdorfstrasse 10
Postfach, 3000
Bern 22 Switzerland

Dear Dr. Gardi:

An inspection was conducted by the Food and Drug Administration (FDA) of the Central Laboratory of the Swiss Red Cross, Wankdorfstrasse 10, Bern, Switzerland, from November 12 to November 20, 1996. During the inspection violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Part 211 and Parts 600-610 were documented as follows:

1. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21CFR 211.160(b)]. For example,

a. a temperature distribution study to assure that all shelves of the lyophilizers obtain and maintain a temperature of -40°C during freeze drying operations has not been performed;
b. the steam sterilization validations for the lyophilizers did not include a heat distribution study to establish and confirm the coldest spot and demonstrate an even heat distribution of the sterilization cycle;
c. there is no enumeration of the biological indicators to assure that there is a quantifiable reduction of a biological challenge for the sterilization cycle of the lyophilizers;
d. lyophilizers are not revalidated on a periodic basis;
e. autoclave validation did not include a heat penetration study to demonstrate that sterilization temperatures are adequate to reduce a known microbial challenge and a description of the load pattern for the sterilization of the stainless steel containers used to transport filled bottles of product;
f. the steam sterilization of the ultrafiltration water system has not been revalidated since the initial 1992 validation;

g. the HEPA filters in the areas and the depyrogenation tunnel are not periodically recertified with dioctylphthalate (DOP) or an acceptable alternate aerosol;
h. a smoke study to demonstrate that the HEPA filtered air maintains a sufficient degree of laminarity within the aseptic filling area has not been performed. Additionally, the smoke study performed for the lyophilization unit did not include the small mobile carts which are used to transfer stainless steel containers with filled bottles from the elevators to the lyophilization units; and
i. the growth promotion tests for media used during environmental monitoring did not include the use of the normal microbial flora commonly recovered and isolated from the various production and support areas.

2. Failure to routinely calibrate, inspect or check equipment according to a written program designed to assure proper performance [21 CFR 211.160(b)(4)]. For example,

a. the temperature probe that monitors the 121°C temperature of the steam sterilization of the ultrafiltration water system has not been calibrated;
b. monitoring devices that record the conductivity of the water system have not been calibrated; and
c. gauges used to measure the pressure of the initial filters for the ion beds and the 0.2µm sterilizing filter of the ultra filtration unit have not been calibrated.

3. Failure to clean, maintain and sanitize equipment at the appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product, to establish written procedures for cleaning and maintenance of equipment and to maintain records [21 CFR 211.67] in that:

a. the lamp of the ultraviolet disinfectant unit was not removed and replaced as required by the manufacturer;
b. there are no cleaning records to document that the various stainless steel connection pipes or flexible transfer hoses which are used in the initial plasma pooling or fractionation operations have been adequately cleaned; and
c. there is no record to document cleaning of the CG polyester sheet for the HEPA filtered air.

4. Failure to establish appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211. 113(b)] in that:

a. there are no air pressure differential measurements taken to assure that the elevator transfer areas maintain a negative pressure relative to the area;
b. there is no record to document that the velocity of air at the aseptic filling area work surface is sufficient;

c. there is no monitoring device for the ozone unit to assure that the maximum level of ozone is maintained in the supply water during the pasteurization operations;
d. flexible hoses approximately four feet in length were permanently attached to the Distillation Units and the Clean Steam Generators, thereby presenting static areas for standing water; and
e. deionized water, instead of water for injection, is used as the final rinse water for washing the finished product glass containers prior to depyrogenation.

5. Failure to have written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100). For example,

a. there is no written procedure to describe calibration or verification of the belt speed in the depyrogenation tunnel;
b. there is no written procedure to describe the preparation of the bacterial endotoxin challenge controls which are used to demonstrate a 3-log reduction of endotoxin in the depyrogenation tunnel;
c. there is no written procedure to describe the visual inspection checks that are performed by personnel of aluminum cap closures to assure that the crimp caps are securely in place;
d. the document describing the steps required to load the bottles of albumin into the pasteurizer and the January 29, 1996, written notification instructing employees that bottles improperly crimped or labeled must be returned for pooling have not been reviewed and approved for incorporation into your firm's Standard Operating Procedures;
e. there is no written procedure to describe the training required for employees performing the visual inspection of containers from either media fill operations or of final products. Additionally, the control standards used to train individuals who perform visual inspections are incomplete in that there are no standards that describe the criteria for sizing and characterizing particulate matter, examples of over or under filled containers or bottles containing glass, metal or rubber contaminants; and
f. written procedures do not include passivation of the water system in the event that additional welding or modifications are performed.

6. Failure to maintain the following records (21 CFR 211.180):

a. identity of individuals performing media fills during aseptic filling and lyophilization operations, simulating shift change operations during media fills, and obtaining media fill volumes by weight ;
b. data demonstrating that the media fill operations were maintained within specifications;
c. the number of bottles of albumin which are improperly crimped and labeled prior to returning the filled product to pooling operations;

d. the identity of the individual recording data from monitoring conductivity and operating pressures of the water system;
e. the time and temperature (70 minutes @121°C) achieved during validation of the steam sterilization of the ultra filtration water system; and
f. there are no records to document that all operators entering the aseptic areas during manufacturing do not exceed the micorbial limits.

7. Failure to routinely calibrate mechanical equipment to assure it will perform its function during manufacture, processing , and packing of a drug product [21 CFR 211.68(a)], in that there has been no reevaluation performed that the settings on the rubber stopper equipment, first set in 1991, continue to be valid settings.

8. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42(c)(10)(v)], in that,

a. the cleaning solutions are not sporicidal even though environmental monitoring data documents the presence of Bacillus species;
b. the study used to support the effectiveness of the cleaning and disinfection solutions is incomplete in that not all of the challenge microorganisms were identified and did not include the use of contaminants that are commonly recovered from the manufacturing areas. Additionally, on numerous occasions, the data documents that the cleaning and disinfection solutions did not eliminate the microbial contaminants;
c. monitoring for microbial levels is not performed for the solution used for cleaning and disinfecting aseptic manufacturing areas; and
d. solutions used for cleaning the aseptic manufacturing areas are not sterilized prior to use.

In addition to the deviations observed during the inspection conducted November 12 to 20, 1996, we wish to address your firm's compliance with the regulations for Adverse Experience Reporting (AER) Requirements for Licensed Biological Products (21 CFR 600.80). As you are aware, a letter dated November 1, 1996, was sent to your firm from the agency regarding your noncompliance with 21 CFR 600.80(c)(1). An evaluation of the AER's submitted in your response dated November 30 and December 16, 1996, indicates that while your labeling states "Though very rare, non-septic incompatibility reactions including...hypotension following administration...have occasionally been observed." , the agency does not agree this statement exempts your firm from reporting these incidents within 15 days as required by 21 CFR 600.80(c)(1). The reactions which occurred are more severe and more specific with regard to hypotension than what would be expected as described in your labeling. Furthermore, the presence of prekallikrein activator (PKA) as an etiologic mechanism is different and more specific compared to the "non-septic incompatibility reactions" described in your labeling.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. United States federal agencies are advised of the issuance of all warning

letters about drugs so that they may take this information into account when considering the award of contracts. In accordance with 21 CFR 600.,10(a), it is your responsibility, as Responsible Head, to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

We acknowledge receipt of your December 16, 1996, written response which addresses the inspectional observations on the FDA Form-483 issued at the close of the inspection. Additionally, we acknowledge receipt of your second written response dated February 5, 1997, which is currently being reviewed. Corrective actions addressed in your letters may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your December 16 response follows, and is numbered to correspond to the items listed on the Form FDA-483:

Validation and Production Operations; Item #2b: Your response does not address the lack of data demonstrating that media fill operations are maintained within the specifications.

Item #4: Your response states that a full qualification of one lyophilizer of each type used will be completed in January 1997. You do not specify if lyophilizers not qualified will continue to be used to manufacture U.S. licensed products until such time as all lyophilizers will be fully qualified. Additionally, please submit the report which was finalized and approved.

Item #5: Upon completion of the validation of the autoclave, please submit your supporting documentation for review.

Item #6: Your response does not address establishment of a written procedure for the preparation of the bacterial endotoxin challenge controls which are used to demonstrate a 3-log reduction of endotoxin.

Water System; Items #1, #4, and #5: Please submit the supporting documentation upon completion of your corrective action for these three items.

Air Handling System; Items #1, #3, and #4. Upon completion of your corrective action for these three items, please submit your supporting documentation. Additionally, your responses for Items #3 and #4 do not address maintaining records of the air velocity measurements at the aseptic filling area's work surface or cleaning of the CG polyester sheets.

Cleaning; Items #1 and #2: Please submit the supporting documentation upon completion of your corrective action for these two items.

Additional Observations; Item #1: In your response it is indicated that the weekly monitoring data show that the microbial and chemical quality of the purified water

corresponds to Water for Injection (WFI) requirements according to USP XXIII. It is not clear if your specifications currently include all USP XXIII specifications for WFI. For example, do your procedures describe LAL testing for the presence of bacterial endotoxin and the specifications? Please comment.

Item #4: Please provide an English translation of attachment 25 which is the system of visualization for storing cleaned small equipment.

Please acknowledge the receipt of this letter in writing, within 15 working days, and include any additional steps you have taken to correct the noted deviations and to prevent their recurrence. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation, seizure, and/or injunction.

Your reply should be sent to my attention in the Office of Compliance, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, HFM-600, Rockville, Maryland, 20852.

Sincerely,

James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation
and Research